IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

ARIA DIAGNOSTICS, INC.,

Plaintiff,

v.

SEQUENOM, INC.,

Defendant.
_____/

No. C 11-06391 SI

PRELIMINARY INJUNCTION ORDER

On June 29, 2011, the Court held a hearing on a motion for preliminary injunction sought by Sequenom, Inc. Having considered the arguments of counsel and the papers submitted, the Court DENIES the motion.

BACKGROUND

In this declaratory judgment action, plaintiff Ariosa Diagnostics, Inc. ("Ariosa," formerly known as "Aria") seeks a declaration that its non-invasive prenatal test ("Harmony Test") using cell-free DNA circulating in the blood of a pregnant woman does not directly infringe or contribute to the infringement of U.S. Patent No. 6,258,540 (the "'540 patent"), licensed by defendant Sequenom, Inc. Sequenom now moves for a preliminary injunction pursuant to Fed. R. Civ. P. 65(a), seeking to enjoin Ariosa from: (1) making, using, selling, offering for sale, or importing into the United States any product or service utilizing the methods of Claims 1, 2, 8, 19-22, 24 or 25 of the '540 patent; and (2) making, using, selling, offering for sale, or importing into the United States the Harmony Test.

1. Factual background

A. The '540 Patent

Sequenom is the exclusive licensee of the '540 patent, which Sequenom licensed from Isis Innovation Limited. *See* Declaration of Derek Tatman [Docket No. 37], ¶¶ 3-4. The '540 patent is entitled "Non-Invasive Prenatal Diagnosis," and was issued to Yuk-Ming Dennis Lo and James Stephen Wainscoat on July 10, 2001. Compl. ¶ 14. The patent "relates to a detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample." '540 Patent, Abstract. "This invention enables non-invasive prenatal diagnosis, including for example sex determination, blood typing and other genotyping, and detection of pre-eclampsia in the mother." *Id*. The '540 patent followed the discovery in 1996-1997 by Drs. Lo and Wainscoat that fetal DNA is detectable in maternal serum or plasma samples in extra-cellular or cell-free form.[1] Declaration of Mark I. Evans [Docket No. 35], ¶¶ 20-21. According to Sequenom, prior non-invasive research had focused on detecting fetal cells in the mother's bloodstream because the presence of cell-free fetal DNA was not known. *Id*. The previously used process of isolating intact fetal cells was labor-intensive and produced unreliable results. Evans Decl. ¶ 40. Therefore, the significance of the discovery by Drs. Lo and Wainscoat was that the process of isolating fetal cells was not necessary because fetal DNA was present outside of cells, as "extracellular" or "cell-free DNA" suspended together with the mother's DNA in the maternal bloodstream. Evans Decl. ¶¶ 53, 57. Relevant for purposes of this motion, the '540 patent claims the following:

> **Independent Claim 1.** A method for detecting a **paternally inherited nucleic acid** of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
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> **amplifying a paternally inherited nucleic acid** from the serum or plasma sample and detecting the presence of a **paternally inherited nucleic acid** of fetal origin in the sample.
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> **Independent Claim 24.** A method for detecting a **paternally inherited nucleic acid** on a

[1] "Nucleic acid" is the overall name for the class of molecules that includes DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). Blood is made up of cells and plasma. Blood plasma is the fluid containing proteins and other molecules in which blood cells are suspended. Serum is plasma without the clotting proteins (platelets), *i.e*., blood minus the blood cells and the clotting factors. *Id.* ¶ 44.

maternal blood sample, which method comprises
removing all or substantially all nucleated and anucleated cell populations from the blood sample,
amplifying a paternally inherited nucleic acid from the remaining fluid and subjecting the amplified nucleic acid to a test for the Paternally [sic] inherited fetal nucleic acid.

Independent Claim 25. A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises
obtaining a non-cellular fraction of the blood sample
amplifying a paternally inherited nucleic acid from the non-cellular fraction, and
performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid.

'540 Patent 23:60-67, 26: 20-36 (the construction of the highlighted terms is disputed by the parties). The challenge posed by obtaining DNA from the mother's blood sample was distinguishing fetal DNA from the mother's DNA. The patent specification states that the "method according to the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother." '540 Patent 2:57-60. The application of the claimed method is illustrated with five studies where a paternally-inherited sequence was used to distinguish the fetal DNA from the maternal DNA.[2]

The '540 Patent application was originally filed in 1998, and underwent two rounds of rejections before the patent issued in 2001. In that process, the PTO required the applicants to include the limitation "paternally inherited" in claims where the applicants had wanted to use simply "nucleic acid" or "foetal nucleic acid." Declaration of Farideh Bischoff [Docket No. 83], Ex. 4 at 41. The proposed amendments were discussed with the PTO largely over the telephone, however, in the Notice of Allowability, the Examiner stated:

> The claims are drawn to a method of detecting paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, by amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited

[2] As examples of the claimed method, the specification includes four published research studies (a similar fifth study is mentioned in passing): 1) analysis of DNA from maternal serum to detect the presence of a Y-specific sequence in order to identify a male fetus; 2) analysis detecting higher rates of Y-specific sequence than in normal samples, demonstrating that the level of fetal DNA in the maternal serum is elevated in pregnancies with an abnormal number of chromosomes in the fetus; 3) pre-natal determination of fetal rhesus blood group (RhD) through detection of RhD-positive sequence when the mother is known to be RhD-negative; and 4) analysis showing elevated fetal DNA levels in maternal serum in pre-eclamptic pregnancies, also by analyzing rates of detecting the Y-specific sequence. All of the studies utilized the existing TaqMan probe system to search for a standard sequence from the SRY gene (a sex-linked gene that appears on the Y chromosome) or the RhD sequence. In the last study, a beta-globin sequence was also used to identify total percentage of DNA in serum and plasma samples. '540 Patent, 4:9-19:8.

> nucleic acid of fetal origin in the sample.
>
> The closest prior art is directed to detecting alterations in plasma DNA for diagnosing and or monitoring the development of DNA (Stroun et al GB2299166, September 1996). The art also teaches detecting fetal cells in maternal blood and performing diagnostic tests on the blood. However, the art does not teach nor reasonably suggest that nucleic acid of fetal origin is present in maternal serum or plasma.

Evans Decl. ¶ 73.

B. The Parties' Diagnostic Tests

Ariosa and Sequenom both developed diagnostic tests that use cell-free DNA to determine whether a fetus is likely to possess an extra copy of certain chromosomes ("trisomy" is a presence of three copies of a chromosome rather than the normal two): trisomy of chromosome 21, which causes Down syndrome; trisomy of chromosome 18 (Edwards syndrome); and trisomy of chromosome 13 (Patau syndrome).[3] Declaration of William Welch [Docket No. 36], ¶ 38; Bischoff Decl. ¶ 116. The risk of fetal chromosomal abnormalities increases with the mother's age in a linear fashion until approximately age 30 and exponentially thereafter. Sequenom identifies mothers over age 35 as "high risk," a category which may also include other risk factors, such as family history. Evans Decl. ¶ 31-32. Detecting fetal DNA in the mother's blood is a significant advantage over the previous invasive methods of obtaining DNA samples, such as amniocentesis or chorionic villus sampling, which require an insertion into a mother's body close to the fetus and may result in loss of the pregnancy. *Id.* ¶ 37. Therefore, many "high risk" women choose not to undergo invasive diagnostic procedures. *Id.* ¶ 36. Further, according to Sequenom, "even the best such tests in practice only have about an 85% detection rate, and false positives are a problem." *Id.* ¶ 33.

Sequenom's MateriT21 test utilizes a DNA sequencing technique called "massively parallel shotgun sequencing" (MPSS), which sequences the DNA in the sample without regard to its

[3] In 95% of cases, Down syndrome is caused by trisomy of chromosome 21. In the other approximately 5% of cases, a chromosomal translocation occurs where an extra chromosome 21 becomes attached (translocated) to another chromosome, in addition to the normal two copies of chromosome 21. Evans Decl. ¶ 28. Trisomy is caused by failure of chromosomes to separate during cell division; in over 90% of the cases, the nondisjunction event occurs in the mother's egg. Bischoff Decl. ¶ 26.

chromosome of origin. Bischoff Decl. ¶ 73. Ariosa's Harmony Prenatal Test has two components. The first component detects rates of sequences associated with chromosomes 21, 18, and 13, using sequences that are identical in all individuals (non-polymorphic) to detect the relative proportion of DNA from these chromosomes (higher than normal rates would indicate extra copies). *Id.* ¶¶ 75-78. The second component analyzes sequences from other chromosomes that are likely to vary between individuals (polymorphic alleles),[4] to determine what percentage of the DNA in the sample comes from the fetus and what percent comes from the mother. *Id.* This information is used to interpret the data from the first component of the test, since only the fetal DNA could have extra copies of the chromosomes in question. *Id.* ¶¶ 90-91. Ariosa named the first component "DANSR" (Digital Analysis of Selected Regions) and the second component "FORTE" (Fetal-fraction Optimized Risk of Trisomy Evaluation). *Id.* ¶¶ 75-78. According to Ariosa, the chromosome-specific method used in the Harmony Test is significantly more efficient than the MaternT21 test because it requires "approximately one million raw reads of DNA sequence per sample [...], whereas MPSS-based approaches involve approximately 25 million raw reads." *Id.* ¶ 24. Ariosa cites studies reporting test sensitivity and specificity for Sequenom's MaterniT21 test at 98.6% and 99.8% respectively, and for Harmony Test at 100% and 99.97% respectively.[5] Declaration of John Stuelpnagel [Docket No. 97], ¶ 18.

Sequenom argues the Harmony Test infringes the '540 patent because by comparing the differences between the maternal and fetal DNA, the Harmony Test identifies paternally-inherited DNA – the method covered by the '540 patent. Ariosa contends that based upon a reasonable construction of the claims in light of the actions of the PTO during the patent prosecution, the Harmony method is not covered by the limitation of detecting a known sequence of "paternally inherited nucleic acid."[6]

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[4] Alleles are different versions of the same gene that account for individual differences such as eye color.

[5] Sensitivity measures the proportion of actual positives that are correctly identified, while specificity measures proportion of actual negatives that are correctly identified. Stuelpnagel Decl. ¶ 10.

[6] The parties also dispute the construction of the term "amplifying" in the claims.

C. The Market

Sequenom asserts that it has invested substantial resources in the process of developing and educating the market for non-invasive detection of fetal aneuploidies (chromosomal abnormalities) in the United States. Sequenom introduced the first version of the MateriT21 test to the market on October 17, 2011, and the expanded MateriT21 PLUS test, which includes the detection of trisomies 18 and 13, was publicly announced on February 8, 2012.[7] Welch Decl. ¶¶ 8,15. Sequenom estimates that there are 750,000 high-risk pregnancies in the United States each year. *Id.* ¶ 13. Currently, Sequenom's marketing focuses on high-risk pregnancies, but it intends to expand the test to lower risk groups "when supported by clinical data from further studies." *Id.* In 2011, Sequenom performed approximately 1,000 MateriT21 tests, or about 80 tests per week. *Id.* ¶ 18. On April 16, 2012 (approximately three months after Ariosa's product announcement), Sequenom issued a press release notifying investors that it was revising upward its internal goal for 2012 sales, from 25,000 to 40,000 tests. Declaration of Ryan Sullivan [Docket No. 98], ¶ 64. Sequenom estimates that "an optimistic high case" is an estimate of 60,000 sales in 2012. Welch Decl. ¶ 22. Sequenom's San Diego laboratory has the capacity to sequence approximately 100,000 patient samples, and Sequenom intends to expand to another facility in North Carolina to handle the expected demand in 2012-2014. *Id.* ¶ 26. The list price for the MateriT21 is three times higher than the list price for the Harmony Test, and the estimated "costs of goods sold" for the MateriT21 test is estimated to be ten times higher than for the Harmony Test. *Id.* ¶¶ 30, 34; *see also* Declaration of Ryan Sullivan [Docket No. 98], ¶ 53.

Ariosa announced the Harmony Test in early January, and began offering the product on March 26, 2012. Sullivan Decl. ¶ 17. On May 7, 2012, Ariosa announced that it has partnered with Laboratory Corporation of America Holdings ("LabCorp") to offer the Harmony Test at LabCorp's 1,700 patient service centers, branches, and labs. *Id.*¶ 17. Ariosa intends to offer the Harmony Test to a broader audience than the group defined as "high risk" by Sequenom. Stuelpnagel Decl. ¶ 23. Ariosa estimates that there are 3,550,000 low-risk pregnancies per year in addition to the 750,000 high-risk pregnancies. Sullivan Decl. ¶ 12. Sequenom asserts that studies for non-high-risk groups are still enrolling, and there

[7] The Court will refer to both versions as the "MateriT21 test."

is insufficient data to justify offering the test to a broader market. Evans Decl. ¶ 150. Ariosa contends that the Harmony Test is affordable, more accurate than other available non-invasive screening tests, and safer than the invasive procedures; therefore, there is no reason to offer it only to women in the "high risk" group as defined by Sequenom. Stuelpnagel Decl. ¶ 26. Ariosa also contends that the Harmony Test has been validated in extensive clinical trials that are not limited to a particular patient population. *Id.* ¶ 28. Further, Ariosa asserts that the American Congress of Obstetricians and Gynecologists recommends offering prenatal testing for chromosomal abnormalities to all pregnant women. *Id.* ¶ 12.

There are also other relevant tests in the market. Verinata Health, Inc. launched a test for trisomies 21, 18, and 13 in March 2012; and Natera, Inc. is currently engaged in clinical testing and plans to launch another trisomy 21 test in 2012. Sullivan Decl. ¶ 19-20. Verinata's Verifi test uses the same MPSS method as the MaterniT21 test. *Id.* ¶ 19. According to Ariosa, Verinata's test will be offered at a list price of less than one-half of Sequenom's MaterniT21, with prices as low as 11% of MaterniT21's list price in some markets. *Id.* ¶ 51. Sequenom identified several other companies with noninvasive prenatal tests for chromosomal abnormalities in its public filings with the SEC: Ikonisys, Inc., Celula, Inc., and Fluidigm, Corp. *Id.* ¶ 21. These tests do not use cell-free fetal DNA (using instead, for example, improved methods for isolating intact fetal cells) but may eventually compete with Sequenom's MaterniT21 test. *Id.* ¶ 21, 32.

2. Procedural background

Ariosa filed this declaratory relief action against Sequenom on December 19, 2011, seeking a declaration that its Harmony Test does not infringe any claims of the '540 patent. Sequenom filed a counterclaim against Ariosa, asserting infringement of the '540 patent. Verinata and Natera have also filed declaratory judgment actions in this Court, seeking judgments that their products do not infringe the '540 patent and asserting that the '540 patent is invalid. *See Natera v. Sequenom, Inc.*, C 12-0132-SI (filed 1/6/12); and *Verinata and Stanford v. Sequenom, Inc.*, C 12-0865-SI (filed 2/22/12). Sequenom has counterclaimed in both suits asserting infringement under the '540 patent. In addition to asserting non-infringement and invalidity under the '540 patent, Verinata also seeks a declaratory judgment that

Sequenom's MaterniT21 violates three patents exclusively licensed by Verinata in the field of genetic analysis by nucleic acid sequencing. Amended Complaint, ¶ 3, [Docket No. 34], Case No. 12-865.

Sequenom has moved for a preliminary injunction only against Ariosa, seeking to stop the sale and marketing of the Harmony Test. Sequenom argues that the Harmony Test infringes the '540 patent, by detecting and amplifying paternally inherited nucleic acids from the fetal DNA. Sequenom also asserts that given the fragile and developing nature of the market for non-invasive prenatal tests, as well as the significant cost and price point differences between its and Ariosa's tests, Sequenom will suffer irreparable injury to its ability to market and sell the MaterniT21 test absent a preliminary injunction.

Ariosa responds that Sequenom has publicly misrepresented the scope of the '540 patent "with the goal of deterring potential competitors from entering the market" for non-invasive pre-natal diagnostic testing. Compl. ¶ 16. Specifically, Ariosa contends that the '540 patent does not cover patentable subject matter under the recent Supreme Court decision *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct.1289 (2012). Ariosa also argues that the Harmony Test does not infringe the '540 patent because its method falls outside of the limitations included in all claims of the '540 patent during the prosecution history in order to overcome rejections by the PTO. Finally, Ariosa asserts that Sequenom has failed to show irreparable injury and points out that since Ariosa's product launch, Sequenom has in fact increased its sales goals and continues to raise capital to support the marketing and sales of MaterniT21.

LEGAL STANDARD

The Court has the authority to grant a preliminary injunction in the exercise of its equitable powers. *See* Fed. R. Civ. P. 65. The Supreme Court has affirmed that traditional principles of equity apply in determination of injunctive relief arising under the Patent Act. *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006). A plaintiff seeking a preliminary injunction must establish (1) a reasonable likelihood of success on the merits; (2) irreparable harm if an injunction is not granted; (3) a balance of hardships tipping in its favor; and (4) the injunction's favorable impact on the public interest. *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1376-76 (Fed. Cir. 2009). The grant or denial of a preliminary injunction under 35 U.S.C. § 283 is within the sound discretion of the

district court acting in equity. *Id.*

With regard to the first factor, establishing a likelihood of success on the merits, the patentee seeking a preliminary injunction "must show that it will likely prove infringement, and that it will likely withstand challenges, if any, to the validity of the patent." *Id.* With regard to the second factor, the Supreme Court's "frequently reiterated standard requires plaintiffs seeking preliminary relief to demonstrate that irreparable injury is *likely* in the absence of an injunction." *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 22 (2008) (emphasis in the original). Finally, "[t]hese factors, taken individually, are not dispositive; rather, the district court must weigh and measure each factor against the other factors and against the form and magnitude of the relief requested." *Hybritech, Inc. v. Abbott Labs.*, 849 F.2d 1446, 1451 (Fed. Cir. 1988).

DISCUSSION

1. Reasonable likelihood of success on the merits

To establish a likelihood of success on the merits, Sequenom must show that (1) it will likely prove that Ariosa's Harmony Test infringes one or more claims of the '540 patent and (2) the infringed claims will likely withstand challenges to validity. *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1374 (Fed. Cir. 2006).

A. Claim construction

Determining infringement is a two-step process. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the meaning and scope of the asserted claims must be determined. *Id.* Second, the properly construed claims must be compared to the accused infringing device. *Id.* Claim construction is a question of law. *Id.* at 977; *see also Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454-56 (Fed.Cir.1998) (en banc). In determining the proper construction of a claim, the court begins with the position that "the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). The court must then consider the intrinsic evidence on record, consisting of the claim language, the patent

specification, and, if in evidence, the prosecution history. *Id.* at 1313; *se e also Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

The parties dispute the construction of two terms: "paternally inherited nucleic acid" and "amplifying," contained in all claims at issue, in the following context:

> **1.** A method for detecting a **paternally inherited nucleic acid** of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
> **amplifying a paternally inherited nucleic acid** from the serum or plasma sample and detecting the presence of a **paternally inherited nucleic acid** of fetal origin in the sample.
>
> **24.** A method for detecting a **paternally inherited nucleic acid** on a maternal blood sample, which method comprises:
> removing all or substantially all nucleated and anucleated cell populations from the blood sample,
> **amplifying a paternally inherited nucleic acid** from the remaining fluid and subjecting the amplified nucleic acid to a test for the Paternally [sic] inherited fetal nucleic acid.
>
> **25.** A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises
> obtaining a non-cellular fraction of the blood sample
> **amplifying a paternally inherited nucleic acid** from the non-cellular fraction and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid.

'540 Patent 23:60-67; 26:20-36 (emphasis showing disputed claim terms).

i. "Paternally Inherited Nucleic Acid"

Sequenom contends that "paternally inherited nucleic acid" should be construed as "a nucleic acid that originated from the fetus and which was inherited from the father." Motion for a Preliminary Injunction ("Motion") at 8. Ariosa argues that claims should be construed as limited to "*known* sequence received only from the father, and not fetal sequence which differs from that of the mother" (emphasis added). Opposition to Motion for Preliminary Injunction ("Oppo.") at 7. Specifically, Ariosa argues the limitation describes a method where a known sequence of paternal DNA is searched for in the plasma sample, rather than analyzing the rates of different alleles in the sample without *a priori* knowledge of which sequence comes from which parent, as the Harmony Test does.[8]

[8] "The Harmony test does not identify nucleic acid of fetal origin *by reference to a sequence known to be possessed by the father* and absent from the mother. Rather, the Harmony test processes *all* [target sequences in the sample and detects relative rates]." Oppo. at 2 (emphasis added); *see also id.* at 7 ("Harmony test does not meet this limitation because it does not detect sequence known to be

The patent specification states that the "method according to the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother." '540 Patent 2:57-60. The application of the claimed method is illustrated with five studies where a sequence known to be paternally-inherited was used to distinguish the fetal DNA from the maternal DNA.[9] Therefore, the question with respect to claim construction is whether "paternally inherited nucleic acids," as used in the claims, implies searching for a sequence that is known in advance to come only from the father and not the mother, or more generally covers detecting differences that would identify the paternally-inherited sequences in the fetal DNA at the conclusion of the analysis. Sequenom argues that the former view would be an improper limitation of the claims. Reply in Support of Sequenom's Motion for Preliminary Injunction ("Reply" [Dkt. 114]) at 7.

In *Seachange Int'l, Inc. v. C-COR, Inc.*, 413 F.3d 1361 (Fed. Cir. 2005), the Federal Circuit affirmed the district court's limitation of the scope of the term "network for data communications" to "point-to-point networks" by implication and because the written description disclosed only point-to-point interconnections. *Id.* at 1369.[10] The Federal Circuit also upheld this limitation as appropriate from the prosecution history of the patent: "[t]he prosecution history constitutes a public record of the patentee's representations concerning the scope and meaning of the claims, and competitors are entitled to rely on those representations when ascertaining the degree of lawful conduct, such as designing around the claimed invention." *Id.* at 1372 (internal citations omitted). In construing the claim, "we consider the prosecution history to determine whether the patentee disclaimed or

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received only from the father; it detects nucleic acid with no regard for whether it was received from the father.").

[9] *See supra*, note 2, referring to '540 Patent, 4:9-19:8.

[10] *See also Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1351-52 (Fed. Cir. 2004) (construing claim to require feature that was "central to the functioning of the claimed invention"); *Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1369-70 (Fed. Cir. 2003) (construing claim to include limitation because "every character of the invention" required that the limitation be part of every embodiment); *Watts v. XL Sys., Inc.*, 232 F.3d 877, 882-83 (Fed. Cir. 2000) (construing claim to include limitation, in part, because specification limited invention to embodiments with that feature); *Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1271 (Fed. Cir. 2001) (construing claim to reflect inventor's consistent usage of claim term in specification); *Toro Co. v. White Consol. Indus.*, 199 F.3d 1295, 1300-01 (Fed. Cir. 1999) (construing claim to require a particular configuration where specification described the importance of the configuration and did not disclose others).

disavowed subject matter, narrowing the scope of the claim terms." *Id.* (internal quotation omitted).[11]

Here, the prosecution history likewise supports including the "known" limitation, and as well as the limitation that the patent does not cover detecting differences between the fetal and maternal DNA in general. In its first rejection, the PTO provided the following explanation of the scope of the enabled claims:

> [T]he specification, while being enabling for a method for detecting the presence of paternally inherited fetal DNA in maternal plasma after 15 weeks of gestation wherein the fetal DNA is from the Y chromosome and for detecting the presence of the RhD gene in maternal plasma from an RhD negative pregnant women after 15 weeks gestation, *does not reasonably provide enablement for a detection method performed on serum or plasma for detecting fetal nucleic acid in general* at any time during pregnancy or associated with disease phenotype in serum. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Bischoff Decl., Ex. 10, Office Action at 5 (emphasis added). The second PTO rejection included the same language verbatim, as well as the following clarification:

> Provided that the skilled artisan obtained a positive result for detection of the nucleic acid, it would require undue experimentation determine whether the nucleic acid was a results [sic] of the maternal DNA found in the maternal plasma or whether in fact the nucleic acid was from the fetus.

Id., Ex. 12, Office Action at 5, 11. Further communications about the amendments indicate that "the Examiner advised that the claims would be allowable if limited to 'paternally inherited' nucleic acid, since the specification is enabling for detecting paternally inherited nucleic acid in maternal serum or plasma." *Id.* Ex. 13 at 3. In short, it appears that the PTO was concerned because there was no enablement of a claim that covered detection of fetal DNA by reference to maternal DNA, given the state of art at that time. Instead, the state of the art only enabled a detection of fetal DNA with reference to a known sequence of paternally inherited DNA, *e.g.*, the Y chromosome or the RhD gene. In light of the record before the Court at this stage of the proceedings – particularly the prosecution record – the Court finds that "paternally inherited nucleic acid" should be construed as "DNA sequence known to

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[11] *See also Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) ("[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be."); *Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed.Cir.2005) ("The purpose of consulting the prosecution history in construing a claim is to exclude any interpretation that was disclaimed during prosecution.").

be received only from the father which is not possessed by the mother."

This conclusion is supported by the prosecution history of the abandoned continuation application of the '540 patent. The continuation claims removed the "paternally inherited" limitation and were repeatedly rejected by the PTO. The PTO explained that these claims were not enabled because "the specification does not describe or discuss[] 'detecting the presence of a fetal nucleic acid which differs from that of the maternal genome'.'' Bischoff Decl., Ex. 31, Final Office Action at 2. Only the limitation to "paternally inherited" made the claim adequately enabled and patentable. The PTO provided two examples of why removing the "paternally inherited" limitation would cover broader scope not enabled by specification, and Sequenom argues that those examples do not narrow the definition in the manner sought by Ariosa.[12] Sequenom's Response to Sur-Reply Brief [Docket 116, Ex. 1] at 4, referring to Evans Supp. Decl. ¶¶ 55-60. However, what is significant is why the patentees sought to remove the "paternally inherited" limitation – because they did not believe that the patent with the limitation covered a test for Down's syndrome – and that the PTO did not think such unlimited claims were enabled. Bischoff Decl. ¶¶ 62-63.

Therefore, for purposes of this motion only and based on the current record: "**paternally inherited nucleic acid**" is construed as **"DNA sequence known to be received only from the father which is not possessed by the mother**."

ii. "Amplifying"

The parties also disagree on the construction of "amplifying." Sequenom argues the term should be construed as "increasing the amount by making copies," while Ariosa argues the proper construction is "increasing the relative concentration of." *See* Motion at 8; Oppo. at 16. Ariosa argues that "because

[12] "[T]he term 'paternally inherited' does not cover the cases: (a) in which a gene is maternally inherited, yet the nucleic acid is not (in total) the same in the fetus as in the mother, and (b) in which the gene is altered spontaneously, for example, in the egg or sperm, i.e. by what appears to be chance or sporadic mutation." Bischoff Decl. ¶ 60. Case (a) is clinically significant because in most cases of Down syndrome, the extra copy of chromosome 21 comes from the mother. The second copy is passed on when there is an improper disjunction of chromosomes during cell division. Thus, the fetal DNA is different from the mother, who has a normal number of chromosomes, but this difference is not one inherited from the father. Case (b) is random mutations which are a very small fraction and are not clinically significant in the diagnostic tests at issue.

the 'amplifying' limitation was added to the claims during prosecution to address the examiner's concern that without an enrichment step the claimed methods were not enabled, increasing the relative concentration of the paternally inherited nucleic acid compared to other nucleic acids in a sample is a necessary part of the proper construction of the limitation." Bischoff Decl. ¶ 122. Sequenom responds that "amplification" has a standard meaning, which is "simply increasing in amount." Oppo. at 3. However, the proper claim construction must look to the meaning of the term in the context of the claim, the specification, and the prosecution history. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Intrinsic evidence, such as the patent language and prosecution history, carries more weight than extrinsic evidence, such as dictionary definitions, because "heavy reliance on the dictionary divorced from the intrinsic evidence risks transforming the meaning of the claim term to the artisan into the meaning of the term in the abstract, out of its particular context, which is the specification. The patent system is based on the proposition that claims cover only the invented subject matter. " *Phillips*, 415 F.3d at1321.

Here, in all the independent claims "amplifying" modifies "a paternally inherited nucleic acid." This construction is not the same as amplifying fetal DNA in general, or all DNA in the sample. Sequenom's own expert, Dr. Evans, testified that amplifying a nucleic acid is equivalent to "enriching"[13] and he has also stated that "[t]he person of ordinary skill in the art would also understand 'foetal DNA enrichment' to have its ordinary and customary meaning of 'increasing the concentration of fetal DNA relative to the maternal DNA in the sample.'" Evans Decl. ¶ 121. Therefore, at this juncture and on the record currently before the Court, the Court finds that "**amplifying a paternally inherited nucleic acid**" should be construed to mean "**increasing the concentration of a paternally inherited nucleic acid relative to the other DNA in the sample.**"

B. Infringement

To find infringement, "the court must determine that every claim limitation is found in the accused device." *Playtex Products, Inc. v. Procter & Gamble Co.*, 400 F.3d 901, 909 (Fed. Cir. 2005)

[13] *See* Bischoff Decl. ¶ 124, quoting Ex. 52, Evans Tr. at 182:8-14 ("Q: Is amplifying DNA the same as enriching DNA? A: Fundamentally.").

(internal citations omitted). The determination of infringement, both literal and under the doctrine of equivalents, is a question of fact. *Lockheed Martin Corp. v. Space Sys./Loral, Inc.*, 324 F.3d 1308, 1318 (Fed. Cir.2003). On a motion for preliminary injunction, if the alleged infringer raises a "substantial question" as to infringement that the "patentee cannot prove 'lacks substantial merit,' the preliminary injunction should not issue." *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350-51 (Fed. Cir. 2001).

Sequenom argues that Ariosa's Harmony Test infringes the '540 patent because the differences detected between maternal and fetal DNA are in fact the "paternally inherited nucleic acids": "[b]ecause the fetus inherits its nucleic acid sequences from the mother and the father, the fetal alleles that differ from maternal alleles will exist on a nucleic acid inherited from the father." Motion at 10. Further, Sequenom's expert argues that "when Ariosa detects an imbalance at one of the specified polymorphic [loci], Ariosa is detecting a paternally inherited nucleic acid from the fetus." Evans Supp. Decl. [Dkt. 114, Ex. 3], ¶ 73. However, Sequenom's argument ignores the importance the PTO placed on "paternally inherited" limitation and the lack of enablement for broader claims. The PTO rejected two rounds of applications that attempted to secure claims without the limitation, covering detection of fetal DNA by any means, rather than only by searching for what is known to be a paternally inherited sequence. Reading the patent to cover the Harmony Test's method, which does not rely on the crucial knowledge of what sequence would be different from the mother's genome in advance, would be contrary to the limitation repeatedly imposed by the PTO. The PTO insisted on the limitation in light of what is actually enabled by the specification– the patentee's a method for detecting fetal DNA by searching for a sequence known to be absent from the mother's genome, and only that method.

Sequenom argues that the Harmony Test still infringes because the alleles are detected by matching them to standard sequences, and thus they are "known" in advance. *Id.* ¶ 74. The claim scope, however, must be examined in light of PTO's previously discussed statement that

> [T]he specification, while being enabling for a method for detecting the presence of paternally inherited fetal DNA in maternal plasma after 15 weeks of gestation wherein the fetal DNA is from the Y chromosome and for detecting the presence of the RhD gene in maternal plasma from an RhD negative pregnant women after 15 weeks gestation, does not reasonably provide enablement for a detection method performed on serum or plasma for detecting fetal nucleic acid in general.

Bischoff Decl., Ex. 12, Office Action at 5. Harmony's method of detecting an imbalance in the proportion of sampled alleles does not rely on searching for a sequence known to be absent from the mother's genome in the manner that the Y chromosome and RhD-positive sequences were known to be absent from the mother's DNA in the examples of the specification. Instead, it is based on statistical analyses of occurrences of generally known sequences at different sites in the entire DNA sample. This is a distinct and novel method of identifying the fetal DNA from the mother's DNA in the sample. Indeed, it appears that the absence of an algorithm such as the one developed by Ariosa is what led the PTO to reject Sequenom's attempt to secure broader claims because they would require "undue experimentation." *See supra*, at 12. That broader scope was attempted again in the continuation application, and was rejected by the PTO as not enabled by the specification: "the specification does not describe or discuss[] 'detecting the presence of a fetal nucleic acid which differs from that of the maternal genome.'" Bischoff Decl., Ex. 31, Final Office Action at 2. Sequenom abandoned this continuation application, and a patentee may not recapture abandoned claim scope. *See e.g., MBO Laboratories, Inc. v. Becton, Dickinson & Co.*, 602 F.3d 1306, 1313 (Fed. Cir. 2010) ("The recapture rule prevents a patentee from regaining through reissue ... subject matter that he surrendered in an effort to obtain allowance of the original claims.") (quoting *In re Clement*, 131 F.3d 1464, 1468 (Fed. Cir.1997)).

In light of the prosecution history, and based on the record that has been developed, the Court finds that Ariosa has raised a "substantial question" as to infringement which Sequenom has not shown "lacks substantial merit."

C. Validity

As with infringement, Ariosa must raise a "substantial question" with regard to the validity or enforceability of the '540 patent, and if it does, Sequenom must demonstrate that those defenses 'lack substantial merit.' *Sanofi-Synthelabo*, 470 F.3d at 1374. If Ariosa raises a "substantial question" concerning validity or enforceability, "the preliminary injunction should not issue." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1364 (Fed. Cir. 1997).

Ariosa argues that the '540 patent does not cover patentable subject matter because it attempts

to claim the discovery that fetal DNA is detectable in maternal serum or plasma samples, which is an unpatentable natural phenomenon under *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012).[14] Ariosa argues that "'540 patent does no more than combine conventional techniques, such as 'amplifying' and 'detecting' certain fetal DNA, with the 'discovery' that this DNA naturally exists in maternal blood." Oppo. at 1. Sequenom counters that the claims "recite specific steps that confine the claims to a specific, useful application." Reply at 8 (quoting *Nazomi Commc'ns, Inc. v. Samsung Telecomms., Inc.*, 2012WL 967968, *4 (N.D. Cal. Mar. 21, 2012)). However, Sequenom's reliance on the *Nazomi Communications* case is inapposite because that case did not concern a discovery of a natural phenomenon, but a programming method described as:

> [T]he claims recite modifying the data in the data structure or constant pool entry, including the data in the resolution data field. The claims also recite specific implementation details, such as using data from the resolution data field as an index to a jump table. Thus, it appears that the claims are directed to a specific application and implementation of general principles, rather than broadly pre-empting the use of an abstract idea.

Id. at *3. In cases more similar to the present one, courts have found that *Prometheus* decision raised a substantial question of validity of an existing patent requiring further deliberation: *Tessenderlo Kerley, Inc. v. Or-Cal*, Inc., C 11-04100 WHA, 2012 WL 2054994 (N.D. Cal. June 5, 2012) ("As discussed, more discovery is needed to determine whether the application of those particulate materials in the manner described was routine and conventional. Until then, this order leaves unanswered whether the patent claims too broadly preempt the use of a natural law."); *Shire LLC v. Impax Laboratories, Inc.*, C 10-5467 RS, 2012 WL 1980803 (N.D. Cal. June 1, 2012) ("That issue, like some of Impax's other arguments, is better addressed at a later stage, as it requires much broader consideration of all the evidence at bar."). In another recent district court case, the challenged patent was held invalid under *Prometheus* on summary judgement. *SmartGene, Inc. v. Advanced Biological Laboratories, SA*, CIV.A.

[14] The Supreme Court held that a diagnostic method based on determination of concentrations of certain drug metabolites in the blood was not patentable because "[i]f a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." *Prometheus Laboratories, Inc.*, 132 S. Ct. at 1297. The Court distinguished the diagnostic method in question from a patentable manufacturing method described in *Diamond v. Diehr*, 450 U.S. 175, (1981) where "other steps apparently added to the formula something that in terms of patent law's objectives had significance – they transformed the process into an inventive application of the formula." *Id.* at 1299.

08-00642 BAH, 2012 WL 1059611 (D.D.C. Mar. 30, 2012) ("As with the claim examined in *Prometheus*, these 'steps consist of well understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately. For these reasons [this Court believes] that the steps are not sufficient to transform unpatentable [abstract ideas] into patentable applications....'").

In the present case, Sequenom asserts that"Dr. Lo's and Dr. Wainscoat's discovery of the presence of cell-free fetal DNA in maternal plasma and serum [. . .] was a pioneering breakthrough for noninvasive prenatal testing." Evans Decl., ¶ 41. However, the steps Sequenom used to enable their method claims in light of the cell-free DNA discovery – namely fractionation (separating blood into cells and plasma), amplification, and detection – are described as "standard" in the patent itself.[15] Ariosa's experts provide further support that these steps were standard methods used for DNA detection and amplification at the time the patent was filed and Sequenom's experts do not provide evidence to the contrary. In the Response to the Sur-Reply, Sequenom again cites the statement of its expert, Dr. Evans, that "many investigators on many research projects – myself included – discarded the plasma fraction, because nobody thought that fetal cell-free DNA would be present." Response to Sur-Reply [Docket 116, Ex. 1] at 2. This statement supports only the significance of the discovery of fetal cell-free DNA – a natural phenomenon; Sequenom has pointed to no specific steps in the method beyond fractionation, amplification, and detection, which are referred to as standard techniques in the patent.[16]

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[15] The '540 patent specification states, for example: "The preparation of serum or plasma from the maternal blood sample is carried out by standard techniques. The serum or plasma is normally then subjected to a nucleic acid extraction process. Suitable methods include the methods described herein in the examples, and variations of those methods." '540 Patent, 2:26-32. "An amplification of foetal DNA sequences in the sample is normally carried out. Standard nucleic acid amplification systems can be used, including PCR, the ligase chain reaction, nucleic acid sequence based amplification (NASBA), branched DNA methods, and so on. Preferred amplification methods involve PCR." '540 Patent, 2:44-47. "Detect" is used broadly throughout, for example: "Real time quantitative PCR analysis was performed using a PE Applied Biosystems 7700 Sequence Detector (Foster City, Calif., U.S.A.) which is essentially a combined thermal cycler/fluorescence detector with the ability to monitor the progress of individual PCR reactions optically. The amplification and product reporting system used is based on the 5' nuclease assay (Holland et al 1991) (the TaqMan assay as marketed by Perkin-Elmer)." '540 Patent, 6:35-45.

[16] Ariosa points out that Sequonem's expert, Dr. Evans, stated as much in his deposition "when he agreed that 'traditional DNA diagnostics well before 1997 traditionally involved three steps . . . [s]ample preparation, amplification, and detection' and 'others before Dr. Lo amplified and detected

At this juncture, the Court is concerned that Sequenom has not put forward substantial evidence that the steps described in the specification are "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Prometheus Laboratories*, Inc., 132 S. Ct. at 1294. Therefore, the Court finds that Ariosa raised a "substantial question" with regard to the validity as well as infringement of the '540 patent.[17]

2. Irreparable Injury, Balance of Hardships and Public Interest

"A party seeking injunctive relief must make 'a clear showing' that it is at risk of irreparable harm, which entails showing 'a likelihood of substantial and immediate irreparable injury.'" *Apple, Inc. v. Samsung Elecs. Co.*, 2012 U.S. App. LEXIS 9720 (Fed. Cir. May 14, 2012) (quoting *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 22 (2008) and *O'Shea v. Littleton*, 414 U.S. 488 (1974)). Sequenom argues that if Ariosa is not enjoined, Sequenom will suffer irreparable price erosion, loss of market share, and damage to its goodwill and reputation as an industry leader.

Because the Court has found that Ariosa raises substantial meritorious questions on infringement and validity,. the preliminary injunction should not issue. *See Amazon.com, Inc. v. Barnesand-noble.com, Inc.*, 239 F.3d 1343, 1350-51 (Fed.Cir. 2001). However, the Court finds – on the limited record before it – that balancing the remaining factors also weighs against issuing a preliminary injunction. With respect to irreparable injury, the Court recognizes that some price erosion will likely result from Ariosa's entry into the market given the significantly higher price of Sequenom's MateriT21 test. However, the degree of that erosion – as well as the impact on Sequenom's market share – has not been adequately demonstrated by Sequenom's damages expert. Sequenom's expert, Dr. Mohan Rao, did not take into account the *actual* market when giving his opinion on Ariosa's future impact on Sequenom's business plan. Specifically, Dr. Rao ignored the presence of Verinata, whose

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nucleic acid in plasma and serum.'" Ariosa's Sur-Reply [Docket 115, Ex. 1] at 2.

[17] Since the Court finds Ariosa has raised substantial questions as to both noninfringement and invalidity under *Prometheus*, the Court need not reach Ariosa's arguments that – if the disputed claims were interpreted as broadly as Sequenom proposes – the claims would not be enabled and the patent would be invalidated as anticipated by Kazakov *et al.*, "Extracellular DNA in the Blood of Pregnant Women." (1995).

product is on the market and uses the same method of analysis (MPSS) as MaterniT21. Sullivan Decl., Ex. 14 at 200:18-201:10 (Dr. Rao failed to analyze and had no opinion as to impact of Verinata on Sequenom's sales); *see also id.*, 20:21-24 (Dr. Rao failed to quantify degree to which Sequenom would experience lost sales). In addition to this significant deficiency, Sequenom also failed to demonstrate that any harm would be irreparable. If Sequenom is correct that its MaterniT21 test will lead to new standard of care for prenatal diagnosis and if Sequenom is correct that the '540 patent means that it will be the "exclusive" purveyor of noninvasive tests using cell-free fetal DNA to detect fetal aneuploidies in the United States,[18] any interim price or market loss due solely to Ariosa is likely reparable.

However, the direct result of a preliminary injunction would be to put Ariosa – whose single product is the Harmony Test – out of business. This would also remove a significantly more efficient, less expensive, and allegedly more accurate test from the market and restrict the access to the noninvasive prenatal nucleic acid tests to only high-risk women.[19] As such both the balance of hardships and the public interest likewise weigh against granting a preliminary injunction.

CONCLUSION

For the foregoing reasons, the Court DENIES Sequenom's motion for a preliminary injunction.

IT IS SO ORDERED.

Dated: July 5, 2012

SUSAN ILLSTON
United States District Judge

[18] Sequenom represents that it intends to grant sublicenses to others who use noninvasive cell-free DNA tests for purposes other than testing for fetal aneuploidies, and to others *outside* of the United States for fetal aneuploidies tests. Tatman Decl., ¶ 15.

[19] Sequenom is currently restricting its test to high-risk women, and market analyses have shown that the low-risk market may not pay the price Sequenom seeks. Welch Decl., ¶ 13; Sullivan Decl., ¶¶ 87-88, 51-52.